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Phase II Trial of Tandem High-Dose Chemotherapy with Autologous Stem Cell Transplantation Followed by Reduced-Intensity Allogeneic Stem Cell Transplantation for Patients with High-Risk Lymphoma

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Many patients with lymphoma relapse after autologous stem cell transplantation (AutoSCT). These patients are often considered for allogeneic stem cell transplantation (AlloSCT) if remission can be achieved. If a tandem approach was organized, some cases of relapse might be prevented. We conducted a phase II trial of tandem AutoSCT followed by reduced-intensity conditioning (RIC) AlloSCT for patients with high-risk lymphoma. High-dose chemotherapy was given with busulfan, cyclophosphamide, and etoposide. AlloSCT was composed of RIC with busulfan/fludarabine and tacrolimus, sirolimus, and methotrexate as graft-versus-host disease (GVHD) prophylaxis. Donors were fully matched related or unrelated donors. AlloSCT was performed any time between 40 days and 6 months after AutoSCT. Forty-two patients were enrolled, and all patients underwent AutoSCT. RIC AlloSCT was performed in 29 patients. In the 29 patients who underwent tandem transplant, median time from AutoSCT to AlloSCT was 96 days (range, 48 to 169). The 6-month cumulative incidence of grades II to IV acute GVHD was 13.8% (90% confidence interval [CI], 5.3% to 26.3%). Cumulative incidence of chronic GVHD at 1 year was 37.9% (90% CI, 23.1% to 52.7%). Nonrelapse mortality at 2 years after AlloSCT was 11.1% (90% CI, 3.5% to 23.6%). At a median follow-up of 30 months (range, 17.1 to 51.5) for the entire group, the 2-year progression-free survival rate was 64% (90% CI, 50% to 75%) and the 2-year overall survival rate was 69% (90% CI, 43% to 85%). For the 29 patients who underwent tandem SCT, the 2-year progression-free survival rate was 72% (90% CI, 55% to 83%) and the 2-year OS rate was 89% (90% CI, 74% to 96%). Tandem AutoSCT–RIC AlloSCT appears to be safe and effective in patients with high-risk lymphoma. Prospective trials using such an approach in specific lymphoma subtypes are warranted.

INTRODUCTION

High-dose chemotherapy with autologous hematopoietic stem cell transplantation (AutoSCT) is a standard component of care for many patients with relapsed/refractory Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Although many patients can achieve durable remissions with AutoSCT, disease relapse remains the principle cause of failure. Many well-defined risk factors are predictive of relapse after AutoSCT, including histology (eg, mantle cell lymphoma [1,2] or peripheral T cell lymphoma [3]), primary refractory disease [4], and early relapse [5].

Allogeneic hematopoietic SCT (AlloSCT) is considered in a subgroup of patients with a chemosensitive relapse after AutoSCT with the goal of achieving a durable remission through an immunologically driven graft-versus-lymphoma effect [6-9]. Increasingly, reduced-intensity conditioning (RIC) approaches have been used for such patients given the

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overall morbidity and mortality experienced with traditional myeloablative regimens in patients with lymphoma, particularly in patients who have undergone a prior AutoSCT. Yet for patients with aggressive lymphoma, the use of RIC regimens might result in early disease relapse before the emergence of an effective graft-versus-lymphoma effect [10,11]. Tandem AutoSCT–RIC AlloSCT could combine the cytotoxicity of AutoSCT with an allogeneic graft-versus-lymphoma effect while decreasing the morbidity and mortality associated with conventional myeloablative AlloSCT. We thus conducted a phase II tandem AutoSCT–RIC AlloSCT trial for patients with high-risk lymphoma.

METHODS

This study was approved by the Institutional Review Board at the Dana-Farber Harvard Cancer Center and conducted at Dana-Farber Brigham & Women's Cancer Center and Massachusetts General Hospital Cancer Center. Informed consent was obtained from all patients. This trial was registered at ClinicalTrials.gov (NCT01181271).

Participants were enrolled between October 2010 and June 2013. Patients were ≥18 years of age and had an Eastern Cooperative Oncology Group performance status score of 0 to 2, a left ventricular ejection fraction ≥ 45%, adequate pulmonary function tests (forced expiratory volume in 1 second, forced vital capacity, and diffusing capacity of the lungs for carbon monoxide all ≥50% of predicted), total serum bilirubin < 2.0 mg/dL, transaminases < 3 times the upper limit of normal, and serum creatinine < 2.0 mg/dL. Disease eligibility was as follows: (1) diffuse large B cell lymphoma (DLBCL) or transformed low-grade NHL with residual disease after at least 6 cycles of anthracycline-based chemotherapy, progressive disease after at least 2 cycles of anthracycline-based chemotherapy, or disease relapse within 12 months after completion of anthracycline-based chemotherapy; (2) indolent B cell NHL refractory to most recent therapy or relapsed within 12 months after most recent therapy; (3) any peripheral T cell NHL (excluding cutaneous T cell lymphoma); (4) mantle cell lymphoma; (5) "double-expressing" DLBCL characterized by concurrent over-expression of BCL-2 and MYC proteins; and (6) HL refractory to at least 1 standard salvage chemotherapy regimen.

The trial did not require that a suitable donor be identified before enrollment. To assess disease response before AutoSCT and AlloSCT, positron emission tomography (PET) was preferred, but standard computed tomography images were allowed.

AutoSCT

Autologous hematopoietic stem cell mobilization was carried out per physician discretion using methods such as chemotherapy with granulocyte colony-stimulating factor (G-CSF), G-CSF alone, and G-CSF with plerixafor. Leukapheresis was performed per institutional standard, and a minimum of 2×10^6 $CD34^+$ cells/kg was required to enroll. Myeloablative conditioning consisted of busulfan (.8 mg/kg i.v. every 6 hours × 14 doses for a total of 11.2 mg/kg i.v. given on days −8, −7, −6, and −5), cyclophosphamide (60 mg/kg/day i.v. on days −3 and −2), and etoposide (30 mg/kg i.v. on day −4) (BuCyE). Busulfan pharmacokinetic levels were not measured, and no dose adjustments were made. All patients were hospitalized from admission until neutrophil engraftment. G-CSF was started on day +1 and given daily until engraftment. Infectious prophylaxis was per institutional norm but included agents against bacteria when neutropenic and varicella-zoster and *Pneumocystis jirovecii* upon discharge.

RIC AlloSCT

Once patients recovered, they were allowed to proceed to RIC AlloSCT 40 to 180 days after AutoSCT. All eligibility tests and disease restaging were repeated, and participants with progressive disease were taken off trial. RIC consisted of busulfan 3.2 mg/kg i.v. (.8 mg/kg i.v. daily × 4 days) and fludarabine 120 mg/m^2 (30 mg/m^2 i.v. daily × 4 days). Donors were 8/8-matched (HLA-A, -B, -C, and -DRB1 by allele level typing) related or unrelated donors. Peripheral blood stem cell products were mobilized with G-CSF and collected by leukapheresis.

Graft-versus-host disease (GVHD) prophylaxis was composed of tacrolimus, sirolimus, and low-dose methotrexate (5 mg/m^2 i.v. given on days +1, +3, and +6). Tacrolimus and sirolimus were both started orally on day −3, and therapeutic trough levels were recommended until day +90; in the absence of active GVHD, they were tapered off by day +180. Prophylaxis against varicella-zoster virus and *P. jirovecii* was continued through at least 1 year after AlloSCT. Cytomegalovirus was monitored routinely after AlloSCT, and significant reactivation was treated pre-emptively.

Statistical Considerations

The primary objective of this study was to assess engraftment after this tandem AutoSCT–RIC AlloSCT approach. The tandem transplant approach was considered feasible if at least 65% of the eligible patients who completed AutoSCT were able to proceed to the allogeneic transplant. It was envisioned that 40 patients would enter the study and undergo AutoSCT. Of these 40, we predicted that 15 would not be eligible to proceed to AlloSCT for various reasons that would not apply toward evaluation of feasibility, including patient choice, lack of a suitable donor, or disease progression. Of these 25 patients, if at least 14 patients proceeded to undergo RIC AlloSCT, this tandem transplant design would be considered feasible.

The primary endpoint of the study was donor stem cell engraftment as measured by peripheral blood all cell chimerism before measurement at day +100 after RIC AlloSCT. Secondary endpoints included incidence of nonrelapse mortality (NRM) at 100 days and 1-year after AlloSCT, 2-year progression-free survival (PFS), 2-year overall survival (OS), cumulative incidence of grades II to IV and III to IV acute GVHD by day +200, and cumulative incidence of chronic GVHD requiring systemic immunosuppression. An early stopping rule was written in the case of excessive NRM where if 3 or more cases of NRM were observed in the first 100 days after RIC AlloSCT in the first 10 patients, the study would be terminated for safety reasons.

RESULTS

AutoSCT

Forty-two 42 patients were enrolled and underwent AutoSCT. Twenty-nine patients proceeded to RIC AlloSCT. Clinical and transplant characteristics are presented in Table 1. Median patient age was 56.5 (range, 22 to 69), and 62% of patients were men. Forty-one patients had various

Table 1
Clinical and Transplant Characteristics of all Patients (n = 42) and Patients Undergoing Tandem Transplant (n = 29)

	All Patients (n = 42)	Patients Undergoing Tandem (n = 29)
Gender (male/female)	26/16	16/13
Median age (range) in years	56.5 (22-69)	56 (22-68)
Diagnosis		
Rel/Ref DLBCL	10	5
Rel/Ref indolent NHL	6	5
Double-Expressing NHL	9	7
Transformed B-cell NHL	8	6
T-cell NHL	4	2
Mantle cell NHL	3	2
Rel/Ref Hodgkin	1	1
Heavy chain disease	1	1
Prior lines of chemotherapy, median (range)	2 (1-6)	3 (1-6)
Disease status prior to ASCT		
PR	21	15
CR	21	14
High-dose chemotherapy for ASCT	BuCyE	BuCyE
Reason for not doing AlloSCT		
Disease progression	6	
Patient choice	4	
No suitable donor	2	
Therapy-related AML	1	
Median days interval between ASCT − RIC AlloSCT (range)		96 d (48-169)
Disease status prior to AlloSCT		
PR		6
CR		23
RIC for AlloSCT		Bu/Flu
GVHD prophylaxis		Tac/Siro/MTX
Donor type		
Matched related donor		16
Matched unrelated donor		13
Median follow-up, months (range)	30.0 (17.1-51.5)	29.5 (17.1-48.0)

Rel/Ref indicates relapsed/refractory; ASCT, autologous stem cell transplant; BEAM, BCNU, etoposide, cytarabine, melphalan; AML, acute myeloid leukemia; RIC, reduced intensity conditioning; Bu/Flu, busulfan/fludarabine; Tac, tacrolimus; Siro, sirolimus; MTX, methotrexate.

histologies of NHL, whereas 1 patient had HL. All patients engrafted both neutrophils and platelets after BuCyE AutoSCT, and no NRM was observed after AutoSCT. Thirteen patients did not proceed to RIC AlloSCT because of disease progression in 6, patient choice in 4, no available suitable donor in 2, and therapy-related acute myeloid leukemia in 1. Three of these patients eventually underwent RIC AlloSCT after other treatments.

RIC AlloSCT

Twenty-nine patients underwent the full tandem AutoSCT–RIC AlloSCT, and their clinical characteristics are shown in Table 1. Sixteen patients received stem cell products from matched related donors, whereas 13 patients were recipients of matched unrelated donor grafts. Before AutoSCT, 14 patients were in complete remission (CR), whereas 15 were in partial remission (PR). Before RIC AlloSCT, 23 patients had achieved CR and 6 were in PR. PET imaging was performed for response assessment in 28 of 29 patients.

The median time from AutoSCT to RIC AlloSCT was 96 days (range, 48 to 169). All patients engrafted successfully, with a day +100 median peripheral blood all-cell donor chimerism of 95% (range, 83% to 99%). Day +100 median peripheral blood T cell chimerism was 80% (range, 38% to 100%). Of the 17 patients who experienced a hematological nadir, time to neutrophil engraftment occurred at a median of 12 days (range, 1 to 18) and time to platelet engraftment occurred at a median of 13 days (range, 9 to 41).

GVHD and NRM

As shown in Table 2, the cumulative incidence by day 180 after AlloSCT of grades II to IV acute GVHD was 13.8% (90% confidence interval [CI], 5.3% to 26.3%). The cumulative 1-year incidence of chronic GVHD requiring systemic immunosuppression was 37.9% (90% CI, 23.1% to 52.7%). There were no deaths from nonrelapse causes before day 100. The 1-year and 2-year cumulative incidences of NRM were 6.9% (90% CI, 1.7% to 17.5%) and 11.1% (3.5% to 23.6%), respectively. Causes of death included sepsis (n = 1), bronchiolitis obliterans (n = 1), and respiratory failure due to *P. jiroveci* pneumonia (n = 1).

Relapse

The 1-year and 2-year cumulative incidences of disease relapse were 13.8% (90% CI, 5.3% to 26.3%) and 17.2% (90% CI, 7.5% to 30.4%), respectively, resulting in 5 total cases of relapse in patients who underwent tandem transplantation. All 5 patients had DLBCL by histology, 3 of whom were transformed from underlying indolent NHL. All were in a partial remission before AutoSCT by PET imaging, and 4 of them did not achieve CR after AutoSCT and were in PR by PET imaging before RIC AlloSCT. Four of these patients received donor leukocyte infusions as part of their salvage therapies after disease relapse and were able to achieve CR. No patient who underwent tandem transplantation has died from causes related to their underlying disease.

Table 2
Outcomes after Tandem ASCT-RIC AlloSCT (n = 29)

Outcome	%
Grades 2-4 acute GVHD*	13.8 (90% CI, 5.3-26.3)
Chronic GVHD requiring systemic immunosuppression†	37.9 (90% CI, 23.1-52.7)
2-year incidence of NRM	11.1 (90% CI, 3.5-23.6)
2-year incidence of relapse	17.2 (90% CI, 7.5-30.4)
2-year PFS	72 (90% CI, 55-83)
2-year OS	89 (90% CI, 74-86)

* Cumulative incidence by day +180.
† Cumulative incidence by 1 year.

Survival

Median follow-up for all surviving patients was 30.0 months (range, 17.1 to 51.5). The estimated 2-year PFS rate for all patients was 64% (90% CI, 50% to 75%) and the estimated 2-year OS rate 83% (90% CI, 70% to 90%) (Figure 1). Median follow-up for survivors after RIC AlloS CT was 29.5 months (range, 17.1 to 48.0). The estimated 2-year PFS rate for patients undergoing the tandem procedure was 72% (90% CI, 55% to 83%) and the estimated 2-year OS rate 89% (90% CI, 74% to 96%) (Table 2, Figure 2). The estimated 2-year PFS rate for patients undergoing AutoSCT alone (n = 13) was 46% (90% CI, 23% to 66%) and the 2-year OS rate 69% (90% CI, 43% to 85%); however, several of these relapses occurred before planned RIC AlloSCT could be performed.

Double-Expressing DLBCL

Of the 9 patients with double-expressing DLBCL, 5 possessed concurrent translocations of both *MYC* and *BCL-2*, 3 had extra copies of *MYC* and a *BCL-2* translocation, and 1 patient had over-expression of both MYC and BCL-2 as assessed by immunohistochemistry. Seven of these patients underwent the tandem procedure, whereas 2 patients received AutoSCT alone. None of these patients experienced disease relapse and 1 patient died from nonrelapse causes.

DISCUSSION

Although many patients with relapsed HL or NHL achieve a durable remission with high-dose chemotherapy and AutoSCT, disease relapse remains a frequent cause of death in this patient population. No consolidative or maintenance therapies administered to patients in remission after AutoSCT have shown an OS benefit to date. We conducted a phase II study of tandem AutoSCT–RIC AlloSCT in patients with various lymphoma histologies that we considered at high risk for recurrence after AutoSCT. Our results validate that this is a feasible approach with acceptable morbidity

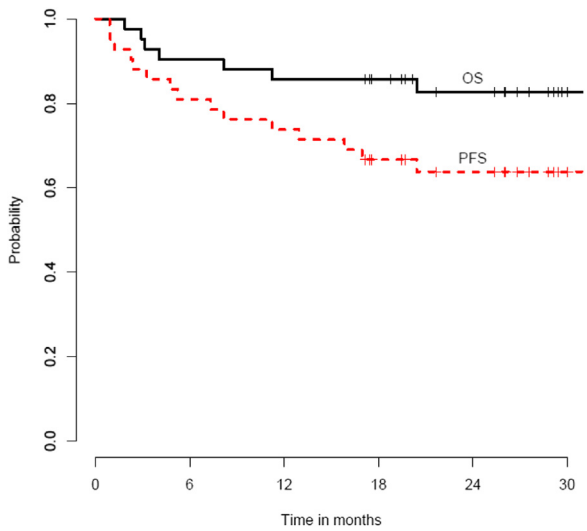

Figure 1. Progression-free and overall survival in all patients (n = 42).

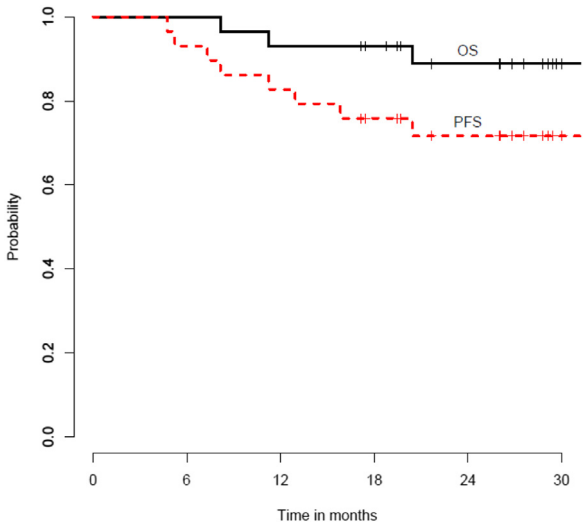

Figure 2. Progression-free and overall survival in patients undergoing tandem transplantation (n = 29).

and mortality in the modern era of transplantation as illustrated by a 2-year NRM rate of 11%. With a median follow-up of 30 months, our estimated 2-year PFS and OS rates for patients who underwent AutoSCT–RIC AlloSCT were 72% and 89%, respectively.

The logic of tandem autologous–allogeneic transplantation is rooted in the ability to deliver both the cytotoxicity of high-dose chemotherapy and the immunologically driven graft-versus-malignancy effect of allogeneic transplantation. Historically, this was provided by conventional myeloablative AlloSCT, yet long-term rates of NRM with myeloablative AlloSCT in patients with lymphoma are unacceptably high [10]. Hence, the tandem approach can hopefully provide similar therapeutic benefits yet minimize treatment-associated morbidity and mortality. This strategy has been widely explored in multiple myeloma with mixed results [12-16]. What is clear from the myeloma experience is that any benefit from a tandem transplant approach will be observed in a high-risk subset of patients, and long-term follow-up is needed to demonstrate such a benefit.

Several series have explored tandem autologous–allogeneic transplantation for patients with lymphoma, and these are summarized in Table 3. Carella et al. [17] first described 15 patients (10 HL, 5 NHL) treated with BCNU, etoposide, cytarabine, and melphalan AutoSCT followed by fludarabine/cyclophosphamide RIC AlloSCT from matched related donors. Eleven patients achieved CR, including 9 patients who were in PR after AutoSCT, and 2 patients died from nonrelapse related causes. Seven patients achieved mixed chimerism and required early immunosuppression withdrawal and/or donor leukocyte infusion to achieve full donor chimerism. Gutman et al. [18] treated 32 patients, 23 of whom underwent the full tandem procedure. Although the early day 100 transplant-related mortality was only 9%, overall transplant-related mortality was quite high at 43% due to GVHD and infectious complications. This resulted in a median PFS and OS of only 157 and 385 days, respectively.

Series published more recently have showed much more promising results. Cohen et al. [19] described 27 patients with advanced follicular NHL (5 with transformed disease) who underwent tandem autologous–allogeneic transplant. With a median follow-up of 39 months, 3-year estimated PFS and OS rates were both 96%. The NRM rate was only 4%, with 1 patient dying from GVHD-related complications. Impressively, no patients experienced disease progression from a cohort with a median of 3 lines of prior therapy, 14 patients in PR, and 5 patients with refractory disease at the time of enrollment. Most recently, Crocchiolo et al. reported outcomes in 34 patients with advanced NHL. With a median

Table 3
Published Experience with Tandem AutoSCT–RIC AlloSCT for Lymphoma

Study	n	Diagnosis	ASCT	RIC AlloSCT	NRM	PFS	OS	F/u
Carella et al. 2000	15	NHL (33%) HL (67%)	BEAM	Flu/Cy	2 pts	5 pts	10 pts	337 d
Gutman et al. 2005	23/32	NHL (84%) HL (16%)	BuCy (22%) BEAM (78%)	TBI or Flu/TBI MRD (65%) URD (22%) UCB (13%)	43%	157 days (median)	385 days (median)	–
Sorror et al. 2009	37	NHL (67%) HL (21%) CLL (12%)	BEAM (48%) CyTBI (52%)	TBI or Flu/TBI MRD (76%) URD (24%)	16%	47% (2-yr)	55% (2-yr)	39 mo
Cohen et al. 2012	27	Follicular NHL (5 transformed)	BEAC (52%) BEAM (48%)	Flu/Cy MRD (100%)	4%	96% (3-yr)	96% (3-yr)	39 mo
Crocchiolo et al. 2013	34	NHL	BEAM (53%) Mel (47%)	Bu/Flu/ATG or Flu/Cy ± thiotepa MRD (85%) URD (15%)	6%	68% (5-yr)	77% (5-yr)	46 mo
Satwani et al. 2014	23/30 (Peds)	HL (53%) NHL (47%)	CBV	Bu/Flu MRD (26%) URD (35%) UCB (39%)	12%	64% (10-yr)	–	60 mo
Wudhikarn et al. 2014	12/34	NHL	–	–	–	37.7 mo (median)	Median not reached	10 mo
Chen et al. 2015	29/42	NHL (98%) HL (2%)	BuCyE	BuFlu MRD (55%) URD (45%)	11.1%	72% (2-yr)	89% (2-yr)	29.5 mo

RIC AlloSCT indicates reduced intensity conditioning-allogeneic stem cell transplantation; F/u, follow-up; Cy, cyclosphosphamide; BuCy, busulfan/cyclophosphamide; TBI, total body irradiation; MRD, matched related donor; URD, unrelated donor; UCB, umbilical cord blood; CLL, chronic lymphocytic leukemia; CyTBI, cyclophosphamide/total body irradiation; BEAC, BCNU, etoposide, ara-C and cyclophosphamide; Mel, melphalan; ATG, anti-thymocyte globulin; BuFlu, busulfan 3.2 mg/kg i.v. (.8 mg/kg i.v. daily × 4 days) and fludarabine 120 mg/m^2 (30 mg/m^2 i.v. daily × 4 days).

follow-up of 46 months, the 2-year transplant-related mortality rate was only 6%, with 5-year PFS and OS rates of 68% and 77%, respectively [20]. Three other tandem transplant lymphoma series have also been presented in preliminary abstract form and are shown in Table 3.

Our study adds to the growing literature of using a tandem transplant strategy for patients with high-risk lymphoma in the modern era and helps to build the rationale to study the efficacy of this approach in a defined homogeneous population. In total, from the 8 series shown in Table 3, 200 patients have now been treated with tandem transplantation for lymphoma. The most recent series, including ours, have found a progressive decrease in overall NRM and an increase in rates of PFS and OS. Indeed, unexpected toxicity and failure of engraftment are no longer concerns with such an approach. These recent improvements likely reflect a combination of several factors, including better patient selection, more accurate HLA matching, improvements in supportive care, and advances in salvage chemotherapy. Not surprisingly, in our series, those who were able to achieve a CR after AutoSCT and before RIC AlloSCT had the best outcomes. In addition, it is notable that 4 of the 5 patients who relapsed after AlloSCT received donor leukocyte infusions as part of salvage therapy to achieve remission again, an option that would not have been available if AlloSCT had not been performed. No patients who underwent tandem transplantation have died from disease progression thus far.

There are several limitations of our study. First, this was a single-arm, phase II trial and, hence, there was no control arm to allow comparison of efficacy. Second, as stated above, the clinical heterogeneity of diagnoses included makes any efficacy endpoint difficult to interpret even compared with historical control subjects. Nevertheless, the relatively low rate of NRM does justify investigating this approach further for patients whose disease response can be maintained long enough to proceed through both transplant procedures. With the advances in alternative donor transplantation over the last decade [21], it is also tempting to include patients who could receive grafts from haploidentical donors or umbilical cord blood, thus overcoming a major obstacle. Nevertheless, given that the leading reason for not being able to undergo AlloSCT on trial was disease progression, it is clear that novel approaches beyond tandem transplantation are needed for a subset of patients whose disease does not optimally respond to AutoSCT.

To truly prove a place for this approach, a prospective study in a defined homogeneous population to test efficacy is needed. Potentially, the appropriate patients are those with relapsed DLBCL in whom the standard of care has remained AutoSCT for the past 2 decades [22], yet durable remission is achieved in only approximately 40% to 50%. Identifying a high-risk subset of such patients has proven challenging. Although the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study highlighted several clinical risk factors that predicted a worse prognosis at the time of relapse [23], it appears that if a CR can be achieved, the prognosis with AutoSCT remains similar to other patients. This has been validated by several single-center series [24-26] as well as a recent study from the Center for International Blood and Marrow Transplant Research registry, which illustrated that disease response to salvage chemotherapy was the most important clinical factor predictive of prognosis for patients undergoing AutoSCT [27]. Including functional imaging into risk stratification may potentially be how we can define a high-risk population as illustrated by our recent series [28], and 1 idea would be to conduct a phase II tandem transplant study in patients with relapsed DLBCL who remain positive by PET imaging after 2 cycles of conventional salvage chemotherapy.

Even with the promising results observed in our series and others, it is important to note that trials of newer therapies such as immunological checkpoint inhibitors [29] or chimeric antigen receptor T cells [30] may obviate the approach of tandem transplantation. Certainly, these therapies appear to be safer in terms of risk for infection and an absence of GVHD; however, long-term follow-up is needed to substantiate efficacy, especially if used as maintenance after AutoSCT. In addition, future comparisons will need to analyze secondary endpoints such as quality of life and cost to appropriately determine which therapies are optimal to administer after AutoSCT in efforts to reduce disease relapse.

In conclusion, high-dose chemotherapy with AutoSCT followed by RIC AlloSCT is a safe and effective therapeutic approach for patients with high-risk lymphoma. It is unclear if certain histological, clinical, or biological subtypes benefit from tandem transplantation compared with AutoSCT or RIC AlloSCT alone. Prospective clinical trials in homogeneous patient populations are warranted to define the place of tandem transplantation in the treatment of patients with lymphoma.

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Authorship statement: Y.C. and E.J. were the principal investigators and take primary responsibility for the study. They designed the research, enrolled patients, analyzed the data, and wrote the manuscript. S.L. designed the research, analyzed the data, and wrote the manuscript. D.C.F., J.D., J.A., P.A., J.B., J.B., C.C., A.E.J., V.T.H., E.H., S.M., R.T., T.R.S., J.H.A., and R.S. enrolled patients and approved the manuscript. C.D.R. coordinated the research and assessed participants.

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